



Assessing adherence to inhaled therapies in asthma and the emergence of electronic monitoring devices

Hetal Dhruve^{1,2} and David J. Jackson^{1,2}

¹Guy's Severe Asthma Centre, Guy's and St Thomas' NHS Trust, London, UK. ²School of Immunology and Microbial Sciences, King's College London, London, UK.

Corresponding author: David J. Jackson (David.jackson@gstt.nhs.uk)



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Technological advancements in the development of electronic monitoring devices allow for identification of intentional and unintentional ICS non-adherence in asthma. <https://bit.ly/37MPYip>

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Abstract

Infrequent use of inhaled corticosteroids (ICS) and/or over-reliance of short-acting β -agonists (SABA) are recognised as key contributors to increased morbidity and mortality in asthma. The most frequent measures of ICS adherence and SABA use rely on patient-reported questionnaires or prescription refill records, neither of which are considered sufficiently reliable. Technological advancements in the development of electronic monitoring of inhaler devices allow for monitoring of use, as well as recording of and feedback on inhaler technique for some devices. Most electronic monitoring devices (EMDs) are paired with a smartphone application, allowing patients to set reminders and display both preventer and reliever use over time. This allows identification of intentional and unintentional ICS non-adherence as well as frequency of SABA use. This information assists clinicians in distinguishing difficult-to-control from severe asthma. Although additional evidence is required to assess the impact of EMDs on clinical outcome measures such as exacerbation rate, the introduction of EMDs into the asthma armoury is a significant step forward in asthma care with the potential to improve asthma-related outcomes.

Introduction

It is estimated that ~500 000 people die of asthma worldwide each year and several independent reviews have highlighted that many of these deaths are preventable [1, 2]. Infrequent use of inhaled corticosteroids (ICS) and/or over-reliance on short-acting β -agonists (SABA) are recognised as key contributors to asthma-related morbidity and mortality [1]. In a landmark study published in 2000, SUISSA *et al.* [3] found that the number of ICS canisters used in the prior year was directly related to the risk of death from asthma. However, despite this and similar reports, adherence to ICS remains poor. Even in the context of the coronavirus disease 2019 (COVID-19) pandemic, ICS adherence rates averaged 55% during 2020, with only 42% achieving the 75% threshold of good adherence [4].

Adherence, often used synonymously with compliance and concordance, refers to the extent to which the recommendations made by a healthcare professional (HCP) regarding medication are accepted and followed by the patient [5]. The adherence process comprises three chronological phases: initiation, implementation and persistence. Initiation is a binary variable, patients either start taking their medication or do not. Implementation refers to whether the dosing corresponds to the prescribed dosing regimen. Lastly, persistence is from the time of initiation to its discontinuation [6]. Most measures of adherence reflect behaviour from a few weeks to 12 months. Persistence over 12 months has been measured in only one study thus far [7].

Non-adherence to medication is either intentional or unintentional. Intentional non-adherence usually reflects a scenario where a patient actively makes a decision to not follow the advice given and does not take their prescribed medication [8]. This may be due to concerns about side effects, the possibility of



addiction or a wish to simply not rely on a medication. Another common and important intentional form of non-adherence may be due to the financial burden of the medication [9]. In contrast, unintentional non-adherence is where the patient fully intends to be adherent to their treatment, but either forgets to use it or, due to poor inhaler technique, a minimal amount of the drug reaches the desired location [5, 8].

Adherence can be assessed in a number of ways, each with their advantages and disadvantages (table 1). Critically, an ideal method of adherence monitoring should be objective, accurate and unobtrusive to

TABLE 1 Measures of adherence

Method of assessment	Examples	Parameter measure	Advantages	Disadvantages
Physician assessment	Questions asked during clinic visit	Indication of non-adherence	<ul style="list-style-type: none"> • Easy to gather information • Quick • Inexpensive 	<ul style="list-style-type: none"> • Subjective • Not standardised • Risk of recall bias
Self-reported questionnaire	Medication Adherence Report Scale for asthma [11], Morisky Medication Adherence Scale [12], Test of Adherence to Inhalers [13]	Pre-established cut-off point determines whether patient is adherent or non-adherent	<ul style="list-style-type: none"> • Easy to use • Inexpensive 	<ul style="list-style-type: none"> • Subjective • Risk of recall and reporting bias leading to overestimation of adherence • Usually only available in English
Prescription database	Medication possession ratio, proportion of days covered	Percentage calculated	<ul style="list-style-type: none"> • Objective • Easy to use • Inexpensive • Adherence can be measured over a long period • Non-adherent patients can be easily identified 	<ul style="list-style-type: none"> • Prescription may not be redeemed • Evidence of dispensed medication does not equate to medication being correctly administered
Dispensing records	Medication possession ratio, proportion of days covered	Percentage calculated	<ul style="list-style-type: none"> • Objective • Easy to use • Inexpensive • Adherence can be measured over a long period • Non-adherent patients can be easily identified • More accurate than a prescription database 	<ul style="list-style-type: none"> • Evidence of dispensed medication does not equate to medication correctly being administered • Prescription may not be redeemed from the same pharmacy each time
Dose counter	Dose counter on inhaler	Comparison of expected to actual dose counter reading	<ul style="list-style-type: none"> • Quick • Easy to use • Inexpensive 	<ul style="list-style-type: none"> • Not on all devices have a dose counter • “Dose dumping” will conceal non-adherence
Type 2 biomarker	F_{ENO} suppression test	Change in F_{ENO}	<ul style="list-style-type: none"> • Objective • Identifies non-adherence when used with DOT • Identifies patients with ICS-resistant Type 2 inflammation who may benefit from biologic therapy 	<ul style="list-style-type: none"> • Cost • Time and resource dependent for patient and HCP • Not widely used
Serum drug level	Serum ICS concentration	Serum concentration	<ul style="list-style-type: none"> • Objective 	<ul style="list-style-type: none"> • Invasive • Cost • Provides short-term recent adherence data only
Electronic monitoring devices	INCA, Propeller, Hailie, Turbu+, Respiro, Herotracker, CapMedic, Digihaler	Frequency of inhaler use	<ul style="list-style-type: none"> • Objective • Some can distinguish between intentional and non-intentional (e.g. error in inhaler technique) non-adherence • Patterns of non-adherence can be identified 	<ul style="list-style-type: none"> • Usually requires the patient to own a smartphone device and be technologically literate • Cost

DOT: directly observed treatment; F_{ENO} : exhaled nitric oxide fraction; HCP: healthcare professional; ICS: inhaled corticosteroids; INCA: Inhaler Compliance Assessment.

minimise impact on patient behaviour [10]. The most widely used adherence measures are patient self-report upon direct questioning and written questionnaires [8]. Questionnaires can be useful in identifying barriers to non-adherence, allowing for personalised interventions to be made. Examples of these include the Medication Adherence Report Scale for asthma [11], the Morisky Medication Adherence Scale [12] and the Test of Adherence to Inhalers questionnaire [13]. However, these subjective measures are not considered particularly robust as it is well known that patients over-report their adherence [14].

The most common objective proxy is calculations of the medication possession ratio or the proportion of days covered, using medication issues as a determinant of adherence. This method has been found to be useful and reasonably accurate [15]. However, a secondary analysis of the Salford Lung Study dataset, which included >4000 asthma patients, found that over 30% of prescriptions issued were not collected from the dispensary [16]. This suggests that prescription records are likely to be an over-estimation of actual adherence. A more accurate measure of adherence may be from dispensing or prescription claim records, provided that prescriptions are redeemed from the same pharmacy each time [17]. Where available, dose counters may also be used to determine adherence as long as patients are on a fixed dose regimen; however, the accuracy of this method can be impacted by dose dumping before clinic visits [8].

The use of serum ICS concentration as a direct measure of adherence has been described with very low ICS concentration levels in patients associated with patients who have poor inhaler technique [18]. In addition, this technique only reflects a recent estimation of adherence and other measures of adherence would be required to confirm longer term ICS use [19]. Hair analysis has also been proposed as a tool for assessing ICS adherence; however, this method is unlikely to become a widely used tool given the increasing availability of electronic monitoring devices (EMDs) [20].

Finally, over the last decade, some specialist asthma centres have incorporated fractional exhaled nitric oxide (F_{ENO}) suppression testing into clinical practice to identify the clinical and biological response to directly observed therapy with ICS. This method allows differentiation between those with ICS-responsive, difficult-to-control but non-severe asthma, from patients with ICS-resistant, severe asthma [21, 22]. Although this has been a huge step forward in both adherence monitoring and improved identification of appropriate patients for biologic therapies, it is both resource- and time-intensive for the patient and clinical team alike.

Consequently, there is a genuine appetite among the clinical community caring for difficult-to-control asthma patients for a cheap, simple, robust measure that can inform the HCP about ICS and SABA use, identify inhaler technique errors, whilst also offering reminders to the patient who is unintentionally non-adherent [23].

Randomised controlled trials (RCTs) including the use of EMDs in children have demonstrated improvements in adherence to ICS, but most trials have not been adequately powered (due to sample size, study duration and/or severity of the cohort) to assess how this relates to clinical outcomes such as exacerbation rate [24, 25]. Clinical trial data including adult asthma subjects have been more promising, with evidence of both improved adherence as well as reductions in SABA use and exacerbation rates [26, 27].

In this review, we report on the new generation of inhaler EMDs (figure 1) that are currently licensed for use or undergoing clinical trial evaluation, identified through PubMed and ClinicalTrials.gov searches. Key search terms included “asthma AND electronic monitoring”.

Inhaler Compliance Assessment™ (INCA) (Dublin, Ireland)

The INCA EMD is one of the most extensively evaluated devices to date [21, 28–35]. However, it is limited for use with the Diskus® inhaler only and a 60-dose memory, meaning it needs to be replaced every 30 days. The device consists of a microphone and a microprocessor that records the audio produced, initiated when the Diskus® inhaler is first opened, with the recording completed when the inhaler is closed [21, 36]. The audio recording includes the click of the Diskus® lever, and then patient exhalation and subsequent inhalation of the medication. Additionally, the amplitude of inhalation is recorded and correlates with peak inspiratory flow. A median amplitude of <0.016 AU corresponds to an inspiratory flow rate of <30 L·min⁻¹, which is deemed insufficient for dry power inhalation [21]. As such, the device identifies critical inhaler technique errors as well as temporal use of the inhaler. This is important as errors can reoccur following an assessment of competence. For example, in one study, despite all patients being judged as initially competent in the use of their inhaler, 17% had >20% errors during the first month of assessment. The majority of patients who made errors did so intermittently [32]. Over the course of the study, the feedback provided by the INCA device led to a reduction in errors to <5%, resulting in observed









Device	Diskus®	Image	Smartphone application	Patient reminder available	Inhaler technique check	Measures inspiratory flow (L·min ⁻¹)
Inhaler Compliance Assessment (INCA) [™] [36]	Diskus®		X	X	✓	✓
Propeller Sensor [38]	pMDI Diskus® Ellipta® Respimat® Breezhaler® Turbohaler® Easyhaler®		✓	✓	X	X
Hailie Sensor® [45]	pMDI Diskus® Turbohaler® Handihaler®		✓	✓	✓	X
Turbu+ [™] [51]	Turbohaler®		✓	✓	X	X
CapMedic® [53]	pMDI		✓	✓	✓	✓
Respiro® [57]	pMDI Ellipta® Nexthaler® Spiromax®		✓	✓	✓	✓
HeroTracker® [59]	pMDI Diskus®		✓	✓	X	X
Digihaler® [61]	Inbuilt Digihaler®		✓	✓	✓	✓

FIGURE 1 Examples of electronic monitoring devices. All device images used with permission of the manufacturer/copyright holder. pMDI: pressurised metered-dose inhalers.

improvements in quality of life. Furthermore, in an RCT, the impact of personalised biofeedback resulted in a significant improvement in adherence compared to a group receiving intensive education in which a fall in the rate of adherence was observed [30].

The usefulness of the INCA monitoring device has also facilitated the interpretation of F_{ENO} suppression testing as it allows the identification of intentional *versus* unintentional non-adherence in patients with apparent ICS-resistant high F_{ENO} [21, 34]. Despite being able to use the inhaler proficiently when initially shown, inadequate inhaler use over a 7-day period was evident in 67% of patients monitored with the INCA device [21]. Similarly, another study of patients with suspected severe uncontrolled asthma found only 27% to have refractory symptoms despite good ICS adherence, whilst 35% were uncontrolled in the context of suboptimal adherence and therefore could be considered difficult to control [30].

The device has a reported failure rate of <2% [21]. The algorithm has demonstrated a sensitivity of 95%, specificity of 94% and an accuracy of 89% in detecting inhalations. Analysis can be performed rapidly, presenting information in real time [21]. Importantly, use of the INCA has been shown to be acceptable to >90% of asthma patients attending a difficult asthma clinic [34].

The INCA device is currently being evaluated for its ability to improve uncontrolled asthma in the INCA device in Symptomatic Uncontrolled Asthma study [37].

Propeller sensor (Propeller Health, Wisconsin, USA)

The Propeller sensor is compatible for use with a wide range of devices, including pressurised metered-dose inhalers (pMDIs) such as Diskus®, Ellipta®, Turbohaler®, Easyhaler®, Breezhaler® and Respimat® [38]. As such, Propeller sensors can be used for both preventer and reliever inhalers to record the date, time and location of actuation [39]. The sensors record when the inhalers are opened and closed as a surrogate for drug delivery, but inhaler technique is not recorded. As well as monitoring use, electronic notifications can be enabled to alert patients and providers about omitted doses.

The sensor transmits information *via* Bluetooth® to a paired smartphone application and securely uploads the data to remote servers. Email notifications or text messages alert individuals and physicians about a change in asthma control based on reliever use. By providing personalised feedback, individuals are enabled to action changes and reduce the risk of an exacerbation [39, 40]. Global positioning system data obtained through a smartphone provides geospatial information with the potential to help patients and HCPs identify asthma triggers. For example, increased SABA use may occur in a certain location associated with high exposure to a particular aeroallergen. When exposed to the same set of triggers in the future, patients are warned of the risk of a possible exacerbation [41].

Propeller sensors have been used in several studies to monitor ICS adherence, including change in ICS use for patients with asthma and COPD during the first few months of the COVID-19 pandemic [26, 42, 43]. In an adult population with uncontrolled asthma, an increase in the percentage of SABA-free days was demonstrated in the group that received reminders and feedback on ICS and SABA use compared to a control group without feedback. Adherence changed minimally in the intervention group, whereas a significant decrease was seen in the control group [27]. This study also identified a positive response in younger participants and those with worse asthma control at baseline, a subset of patients who are likely to particularly benefit from EMDs [27].

The evidence supporting the impact of the propeller sensor on asthma-related emergency department (ED) visits and hospitalisations is mixed. A study of 224 participants aged 3–88 years reported a reduction in asthma-related ED visits and hospitalisations with use of the EMD; however, a Hawthorne effect could not be excluded [26]. In contrast, a paediatric study of 252 participants reported significantly higher rates of asthma-related hospitalisations and ED visits at 12 months for those using EMDs [44]. This was believed to be due to increased feedback when >4 SABA inhalations per day were used, and alerts enabling detection of loss of asthma control directing children to the ED. Additionally, increased vigilance and awareness of clinically concerning symptoms were thought to have prompted increased healthcare utilisation during the study [44].

Hailie® (Adherium, Auckland, New Zealand)

SmartTrack, SmartInhaler and SmartTurbo have been developed and rebranded as the Hailie® sensors.

Similar to the Propeller sensor, the Hailie® sensor can track both preventer and reliever use, logging the date and time of inhaler actuation. The Hailie® sensor is paired *via* Bluetooth® to a smartphone application

and provides notifications and reminders. The application shows bar charts providing instant feedback on adherence and reliever use, which can be sent to an HCP portal through a secure cloud [25, 45]. The Hailie® sensor is currently limited to use with pMDI, Diskus® and Turbohaler® devices. The next-generation Hailie® sensor (currently only available for Symbicort® hydrofluoroalkane) also includes physiological measures that detect inspiratory flow, inhaler shaking and inhaler orientation [45].

The SmartTrack device clips around a pMDI and has been shown to improve adherence to ICS in both adult and paediatric asthma patients [46, 47]. MORTON *et al.* [47] reported a statistically significant improvement in ICS adherence in 77 children. Although this did not translate into a significant improvement in asthma control, children in the intervention arm experienced fewer exacerbations requiring oral corticosteroids at 12 months [47]. A further study of 220 children with asthma reported significant improvements in both ICS adherence and SABA use when compared to baseline and control groups [48].

JOCHMANN *et al.* [49] have used EMDs in the setting of a tertiary paediatric asthma centre to differentiate severe therapy-resistant asthma from difficult-to-control asthma. The authors highlighted that adherence rates only improved for some patients and not for others, suggesting that EMDs may not change behaviour in individuals who are intentionally non-adherent.

The SmartTurbo, which is specifically for use with the Turbuhaler® device, is able to detect the presence or absence of the cap on the mouthpiece of the inhaler. The device records pairs of anticlockwise and clockwise turns as inhaler actuations, and data is uploaded to a database [50]. Use of the SmartTurbo has been validated by comparing actuations recorded on the EMD to paper diaries and found to be highly sensitive over a 12-week period [50].

Turbu+™ (AstraZeneca, Cambridge, UK)

The SmartTurbo/Hailie EMD has been used by AstraZeneca to launch Turbu+. The Turbu+ consists of three components, an electronic device that attaches to a Turbuhaler®, an application for the patients and an online portal allowing HCPs access to the same actuation data [51]. During inhalation, the date and time of actuation is recorded, but inhaler technique is not assessed. Scheduled reminders can be set by the patients and, if a dose is not taken 30 after the scheduled inhalation, a “missed-medication” motivational message is sent automatically. Patients also receive a weekly motivational push notification in the application (*e.g.* “Great week. You’ve been following your prescription this week! Keep it up!”) [52].

In a small real-world study including 32 adult asthma patients, the number of actuations recorded by the EMD was compared to patient-reported inhalations. A total of 932 medication doses were verified by the EMD with a total of 796 doses (85.4%) registered by the patient. A false-positive rate of 3.5% was registered (patient-recorded but not EMD-recorded) as well as a false negative rate of 11.1% (EMD-recorded but not patient-recorded). The reminders and motivational messages were only found to be useful in 50% of patients; however, this study was limited in length (14–21 days) and the patient cohort reported high levels of adherence prior to the study [52].

Capmedic® (Cognita Labs, California, USA)

CapMedic® is an EMD which uses animation with lights and sounds to guide the user through correct inhaler use, recording the seven steps of inhalation, including the mean inspiratory flow rate ($L \cdot \text{min}^{-1}$). It fits onto most pMDIs and provides prompts based on the user’s actions; for example, to guide the user to shake their inhaler correctly. It also detects the user’s breathing and nudges the patient with audio-visual cues to press the inhaler while breathing in, followed by reminders to encourage a long inhalation. Light-emitting diode lights then provide the user with immediate feedback on how well the inhaler was used. As with many of the new EMDs, data is synced to an application providing data on both use and critical errors. The CapMedic® can also provide lung function measurements including peak inspiratory flow and spirometry. It is currently only available for use with pMDIs [53].

In a small study of 23 patients with asthma and COPD, the CapMedic® EMD identified that 100% of patients made at least one error and 74% made at least three errors in using a pMDI [54]. The CapMedic® tool was considered to be more sensitive in identifying and quantifying these errors than observation alone. Another small study of 16 patients showed improved inhaler technique in patients using CapMedic®, compared to patients who were only shown an inhaler technique video [55]. The impact of using the CapMedic® device on other clinical outcomes has not yet been evaluated.

Respiro® (Amiko Digital Health Ltd, Milan, Italy)

The Respiro® sensor records both inhaler administration and technique, and is available for use with pMDI, Ellipta®, Nexthaler® and Spiromax® devices as an add-on sensor providing digital feedback for each critical step of inhalation, including inspiratory flow and inhaler orientation. Data regarding inhaler use is stored and wirelessly exchanged with a paired smartphone or PC reporting adherence patterns and inhaler technique [56]. The Respiro® mobile application provides personalised guidance to help patients manage their condition and is accessible to the HCP [57]. The provider portal displays a dashboard of patient data, notifications about patients at risk of an exacerbation and monthly reports on patient progress, allowing the monitoring of large patient populations. A study evaluating its use is currently underway in children with uncontrolled asthma (Dutch Trial Register NL7705) [58].

Herotracker® (AptarPharma, Milton Keynes, UK, formerly Cohero Health, New York, USA)

The HeroTracker®, linked by Bluetooth® to the BreatheSmart® application, allows tracking of medication use, symptoms and triggers. The application sends daily reminders and information about environmental conditions to alert patients of any changes. The Herotracker® is designed for both controller and rescue medications and fits most pMDI and Diskus® inhalers. The next-generation pMDI add-on is called HeroTracker® Sense and is designed to detect and record co-ordination, flow rate and duration of inspiration. This is then fed back to patients *via* the BreatheSmart application and to the HCP portal. A sensor embedded within a pMDI, called an eMDI, has also been developed [59]. In addition, patients can be issued a linked lung function sensor to track peak expiratory flow rates and forced expiratory volume in 1 s over time. The application keeps a record of the best peak flow and reports how each measurement compares to the best value [59]. Clinical trials evaluating the HeroTracker® and BreatheSmart application are currently underway (ClinicalTrials.gov NCT03103880 and NCT0373486).

Digihaler® (TEVA, Tel Aviv, Israel)

The Digihaler® includes an imbedded inhalation flow sensor that detects inhaler use, recorded when the cap is opened or the patient inhales. Inspiratory flow rates are measured and categorised as good ($>45 \text{ L}\cdot\text{min}^{-1}$), fair ($30\text{--}45 \text{ L}\cdot\text{min}^{-1}$), low or no inhalation ($<30 \text{ L}\cdot\text{min}^{-1}$), assisting identification of poor technique. A recent study reported a strong correlation between the peak inspiratory flow measurements by the Digihaler® and an inhalation profile recorder [60].

Patients can receive notifications and reminders from their Digihaler® application and data on inhaler use can be shared on the screen during an HCP visit or in the form of a PDF summary [61]. It is available for salbutamol (ProAir Digihaler) fluticasone/salmeterol (AirDuo Digihaler) and fluticasone (ArmonAir Digihaler).

In a 12-week, open-label study, use of the ProAir Digihaler highlighted that the strongest predictive factor during the 5 days before an asthma exacerbation was the average number of SABA inhalations per day [62]. A number of additional clinical trials to assess its use are currently underway (ClinicalTrials.gov NCT04896645 and NCT04997304). The Digihaler® is currently only available in the USA.

Limitations of EMDs

To date, mechanical issues have limited the usability of some EMDs. For example, an RCT of 89 paediatric subjects reported that 31 devices broke, with 19 damaged beyond repair [45]. In another study, only 56/102 children had a functional EMD at 12 months [44]. However, in adult studies, this seems to be less of a problem, with only 1.9% malfunctioning and 3.5% lost when assessing over 2500 monitors [63]. Battery life may additionally impact EMD usability, but newer devices now have batteries lasting up to 12 months. A second important factor to consider is the time and staffing required to monitor patients remotely and respond to any alerts if the EMD offers this capability. Lastly, as many EMDs share real-time data to HCPs, data privacy and the need to comply with General Data Protection Regulation (GDPR) requirements must be considered.

Summary

Recent years have seen an exponential growth in the number of EMDs being developed for patients with airways disease. Devices that started as simple counting tools have now been replaced by highly sophisticated inhaler attachments providing audio-visual reminders, guided inhaler use, inspiratory flow measurements and personalised feedback to patients; whilst offering HCPs detailed insights into patient behaviour. Although experience in their use is only now starting to expand from the research space into routine clinical care, EMDs have the potential to improve the quality of care an HCP is able to deliver for patients with asthma. Some EMDs can provide feedback on the elements of inhaler technique that are often difficult to objectively assess, such as whether there was sufficient co-ordination with inhalation or

whether sufficient inspiratory force was generated. The combination of both temporal and inhaler technique data provides a composite account of adherence, allowing identification of both intentional and non-intentional non-adherence over time. Critically, this information can assist clinicians in distinguishing difficult-to-control from severe asthma, which will allow appropriate patient-centred interventions and may avoid inappropriate escalation of therapy to systemic corticosteroids and/or expensive biologic agents. Whilst very promising, additional research is needed to convincingly demonstrate that improvements in adherence to ICS using an EMD translate into clinical outcomes such as exacerbation rate and quality-of-life measures.

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